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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,618	09/19/2008	Antonino Cattaneo	128.1008	5926

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LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER
NOAKES, SUZANNE MARIE

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
06/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/583,618	**Applicant(s)** CATTANEO ET AL.
	Examiner SUZANNE M. NOAKES	**Art Unit** 1656

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 June 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/SUZANNE M NOAKES/
Primary Examiner, Art Unit 1656

Applicant's have acknowledged the previous response erroneously recited Queen in view of Ramsland et al. rather than Pedersen et al. in view of Ramsland et al.

Applicants traverse the rejection of claims 1, 2 and 24 as being obvious over Pedersen et al. in view of Ramsland et al. by stipulating that the method of Pedersen et al. in not applicable to the instant claims because Pedersen et al. describe a method of antibody CDR resurfacing which is not compatible with the instant method.

However, the Examiner would like to point out dependent claim 24 and retromutating amino acids suggests the method (which comprises, e.g. can have additional steps) is precisely in line with the instant method of Pedersent et al. and Ramsland et al.

To further expand on the teachings of Ramsland et al., they do utilize and teach CDR grafting, e.g. exchanging entire CDR regions. "Four main approaches have been used in reducing the immunogenicity of murine antibodies."

"This lead to the production of 'humanized' antibodies, where the sequences for the murine CDRs were introduced into an environment of human framework regions (Jones et al., 1986; Riechmann et al., 1988; Co et al., 1991)."

"Thus, for the immediate future most of the therapeutic antibodies will be prepared by humanization procedures such as CDR grafting."

Thus, one skilled in the art would substitute the method of CDR grafting for CDR resurfacing, although maintain using frameworks as in Pedersen et al., just frameworks based upon crystallographic structures for the reasons recited previously and below.

Applicants further argue that Ramsland et al. use a posteriori crystallographic information for determining the merits of comparing crystallographic structures. And that the only one example showed the failures of others in the field.

However, the Examiner takes the different position that Ramsland et al. teach why it is necessary to compare the 3-D structures and sequences of antibodies to by humanized and CDR grafted; e.g. that it is absolutely necessary to do so when one would select frameworks because they demonstrate that even in a loop region on the VH region having 100% identity from mouse to human, this was not enough to give rise to absolute conservation of the 3-D structure, rather, upon inspection and overlay of the structures (which is produced by a LSQ method and ultimately gives rise to rmsd calculations), it was suggested retromutation was necessary of a proline residue for a serine residue which ensured structural integrity. Thus, this would make obvious, that the very well-known method of CDR grafting would be better served by crystallographic structure comparisons (in addition to sequence identity) and that simple homology models are not sufficient to reveal subtle differences even in sequences which are identical – albeit grafted onto different frameworks.

Finally Applicants argue that a key element of the instant claims is that frameworks which are used are the result of RMS calculations of no more than 2 angstroms and that no where does Pedersent et al. teach any of this. The Examiner would like to direct Applicant's attention to Example 2:

"All four models were subjected to both restrained and unrestrained energy minimization using the DISCOVER (TM Biosym Technology) potential with 300 cycles of steepest descents, followed by conjugate gradient minimization until convergence to within 0.01 Kcal occurred.

The resolution and R-factors of the x-ray structures are given in Table 3 together with the parent frameworks selected in building the models. The structures and models were compared by global fits of the loops. The beta.-barrel strands 1 to 6, as described above, were least squares fitted and the RMS deviation was then calculated over the loops. The backbone (N,C.alpha.,C) RMS values for fitting model and crystal structure frameworks were between 0.4 and 0.9 .ANG., illustrating the conservation of the core .beta.-barrel. Using all eight strands RMS deviations between 0.6 and 1.2 .ANG. were observed." - see Ex. 2, col 31.

Thus, given what is taught by both Pedersen et al. and especially that of Ramsland et al., the combined references make obvious the instant claims and the rejection is maintained.